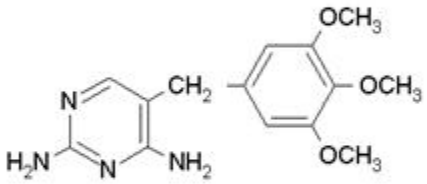
UNIPRIM POWDER FOR HORSES - trimethoprim and sulfadiazine powder
Macleod Pharmaceuticals Inc.

DESCRIPTION
UNIPRIM POWDER contains 67 mg trimethoprim and 333 mg sulfadiazine per gram.
UNIPRIM POWDER is a combination of trimethoprim and sulfadiazine in the ratio of 1 part to 5 parts by weight, which provides effective antibacterial activity against a wide range of bacterial infections in animals.
Trimethoprim is 2,4 diamino-5-(3, 4, 5-trimethoxybenzyl) pyrimidine.



ACTIONS
Microbiology: Trimethoprim blocks bacterial production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase.
Sulfadiazine, in common with other sulfonamides, inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid.
Trimethoprim/sulfadiazine thus imposes a sequential double blockade on bacterial metabolism. This deprives bacteria of nucleic acids and proteins essential for survival and multiplication, and produces a high level of antibacterial activity which is usually bactericidal.
Although both sulfadiazine and trimethoprim are antifolate, neither affects the folate metabolism of animals. The reasons are: animals do not synthesize folic acid and cannot, therefore, be directly affected by sulfadiazine; and although animals must reduce their dietary folic acid to tetrahydrofolic acid, trimethoprim does not affect this reduction because its affinity for dihydrofolate reductase of mammals is significantly less than for the corresponding bacterial enzyme.
Trimethoprim/sulfadiazine is active against a wide spectrum of bacterial pathogens, both gram-negative and gram-positive. The following *in vitro* data are available, but their clinical significance is unknown. In general, species of the following genera are sensitive to trimethoprim/sulfadiazine:

Very Sensitive	Sensitive	Moderately Sensitive	Not Sensitive
Escherichia	*Staphylococcus*	*Moraxella*	*Mycobacterium*
Streptococcus	*Neisseria*	*Nocardia*	*Leptospira*
Proteus	*Klebsiella*	*Brucella*	*Pseudomonas*
Salmonella	*Fusiformis*		*Erysipelothrix*
Pasteurella	*Corynebacterium*		
Shigella	*Clostridium*		
Haemophilus	*Bordetella*		

As a result of the sequential double blockade of the metabolism of susceptible organisms by trimethoprim and sulfadiazine, the minimum inhibitory concentration (MIC) of trimethoprim/sulfadiazine is markedly less than that of either of the components used separately. Many strains of bacteria that are not susceptible to one of the components are susceptible to trimethoprim/sulfadiazine. A synergistic effect between trimethoprim and sulfadiazine in combination has been shown experimentally both *in vitro* and *in vivo* (in dogs).

Trimethoprim/sulfadiazine is bactericidal against susceptible strains and is often effective against sulfonamide-resistant organisms. *In vitro* sulfadiazine is usually only bacteriostatic.

The precise *in vitro* MIC of the combination varies with the ratio of the drugs present, but action of trimethoprim/sulfadiazine occurs over a wide range of ratios with an increase in the concentration of one of its components compensating for a decrease in the other. It is usual, however, to determine MIC's using a constant ratio of one part trimethoprim in twenty parts of the combination.

The following table shows, MIC's using the above ratio, of bacteria which were susceptible to both trimethoprim (TMP) and sulfadiazine (SDZ). The organisms are those most commonly involved in conditions for which trimethoprim/sulfadiazine is indicated:

AVERAGE MINIMUM INHIBITORY CONCENTRATION (MIC-mcg/mL)				
Bacteria	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
Escherichia coli	0.31	26.5	0.07	1.31
Proteus species	1.30	24.5	0.15	2.85
Staphylococcus aureus	0.60	17.6	0.13	2.47
Pasteurella species	0.06	20.1	0.03	0.56
Salmonella species	0.15	61.0	0.05	0.95
β Streptococcus	0.50	24.5	0.15	2.85

The following table demonstrates the marked effect of the trimethoprim and sulfadiazine combination against sulfadiazine-resistant strains of normally susceptible organisms:

AVERAGE MINIMUM INHIBITORY CONCENTRATION OF SULFADIAZINE-RESISTANT STRAINS (MIC-mcg/mL)				
Bacteria	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
Escherichia coli	0.32	>245	0.27	5.0
Proteus species	0.66	>245	0.32	6.2

Susceptibility Testing: In testing susceptibility to trimethoprim/sulfadiazine, it is essential that the medium used does not contain significant amounts of interfering substances which can bypass the metabolic blocking action, e.g., thymidine or thymine.

The standard SxT disc is appropriate for testing by the disc diffusion method.

Pharmacology: Following oral administration, trimethoprim/sulfadiazine is rapidly absorbed and widely distributed throughout body tissues. Concentrations of trimethoprim are usually higher in tissues than in blood. The levels of trimethoprim are high in lung, kidney, and liver, as would be expected from its physical properties.

Serum trimethoprim concentrations in horses following oral administration indicate rapid absorption of the drug; peak concentrations occur in 1.5 hours. The mean serum elimination half-life is 2 to 2.5 hours. Sulfadiazine absorption is slower, requiring 2.5 to 6 hours to reach peak concentrations. The mean serum elimination half-life for sulfadiazine is 4 to 5.5 hours.

Usually, the concentration of an antibacterial in the blood and the *in vitro* MIC of the infecting organism indicate an appropriate period between doses of a drug. This does not hold entirely for trimethoprim/sulfadiazine because trimethoprim, in contrast to sulfadiazine, localizes in tissues and therefore, its concentration and ratio to sulfadiazine are higher there than in blood.

The following table shows the average concentration of trimethoprim and sulfadiazine, as measured in either serum or plasma, in twenty-four adult horses observed after a single dose of Uniprim Powder:

AVERAGE SERUM/PLASMA CONCENTRATION (mcg/mL)									
Trimethoprim (5 mg/kg)					Sulfadiazine (25mg/kg)				
1 hr	3 hr	6 hr	10 hr	24 hr	1 hr	3 hr	6 hr	10 hr	24 hr
0.82	0.69	0.36	0.12	<.025	9.9	18.8	17.3	9.0	1.6

Excretion of trimethoprim/sulfadiazine is chiefly by the kidneys, by both glomerular filtration and tubular secretion. Urine concentrations of both trimethoprim and sulfadiazine are severalfold higher than blood concentrations. Neither trimethoprim nor sulfadiazine interferes with the excretion pattern of the other.

INDICATIONS AND USAGE

Trimethoprim/sulfadiazine is indicated in horses where potent systemic antibacterial action against sensitive organisms is required.

Trimethoprim/sulfadiazine is indicated where control of bacterial infections is required during treatment of:

Acute Strangles	Acute Urogenital Infections
Respiratory Tract Infections	Wound Infections and Abscesses

Trimethoprim/sulfadiazine is well tolerated by foals.

CONTRAINDICATIONS
Trimethoprim/sulfadiazine should not be used in horses showing marked liver parenchymal damage, blood dyscrasias, or in those with history of sulfonamide sensitivity.

WARNING
Do not use in horses intended for human consumption.

ADVERSE REACTIONS
No adverse reactions of consequence have been noted following administration of trimethoprim/sulfadiazine. During clinical trials, one case of anorexia and one case of loose feces following treatment with the drug were reported.
Individual animal hypersensitivity may result in local or generalized reactions, sometimes fatal. Anaphylactoid reactions, although rare, may also occur. **Antidote:** Epinephrine.

PRECAUTION
Water should be readily available to horses receiving sulfonamide therapy.

TOXICITY AND SIDE EFFECTS
Toxicity is low. The acute toxicity of trimethoprim/sulfadiazine is more than 5 g/kg orally in rats and mice. No significant changes were recorded in rats given doses of 600 mg/kg per day for 90 days.
Horses treated intravenously with trimethoprim/sulfadiazine 48% injection have tolerated up to five times the recommended daily dose for 21 consecutive days without clinical effects or histopathological changes.
Lengthening of clotting time was seen in some of the horses on high or prolonged dosing in one of two trials. The effect, which may have been related to a resolving infection, was not seen in a second similar trial.
Slight to moderate reductions in hematopoietic activity following high, prolonged dosage in several species have been recorded. This is usually reversible by folinic acid (leucovorin) administration or by stopping the drug. During long-term treatment of horses, periodic platelet counts and white and red blood cell counts are advisable.

TERATOLOGY
The effect of trimethoprim/sulfadiazine on pregnancy has not been determined. Studies to date show there is no detrimental effect on stallion spermatogenesis with or following the recommended dose of trimethoprim/sulfadiazine.

DOSAGE AND ADMINISTRATION
The recommended dose is 3.75 g trimethoprim/sulfadiazine per 110 lbs (50 kg) body weight per day. Administer trimethoprim/sulfadiazine Powder orally once a day in a small amount of palatable feed.
The usual course of treatment is a single, daily dose for five to seven days.
Continue acute infection therapy for two or three days after clinical signs have subsided.
If no improvement of acute infections is seen in three to five days, re-evaluate diagnosis.
Trimethoprim/sulfadiazine may be used alone or in conjunction with intravenous dosing. Following treatment with trimethoprim/sulfadiazine 48% injection, therapy can be maintained using oral powder.
A complete blood count should be done periodically in patients receiving trimethoprim/sulfadiazine for prolonged periods. If significant reduction in the count of any formed blood element is noted, treatment with trimethoprim/sulfadiazine should be discontinued.

HOW SUPPLIED
Uniprim Powder is available in 37.5 g packets, 1125 g packets, 200g jars, 400g jars, 1200 g jars, 2000 g pails and 12 kg boxes.

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
ANADA # 200-033, approved by FDA

Macleod Pharmaceuticals, Inc.
Fort Collins, CO 80525 U.S.A.

UP093759 Rev. 9/07

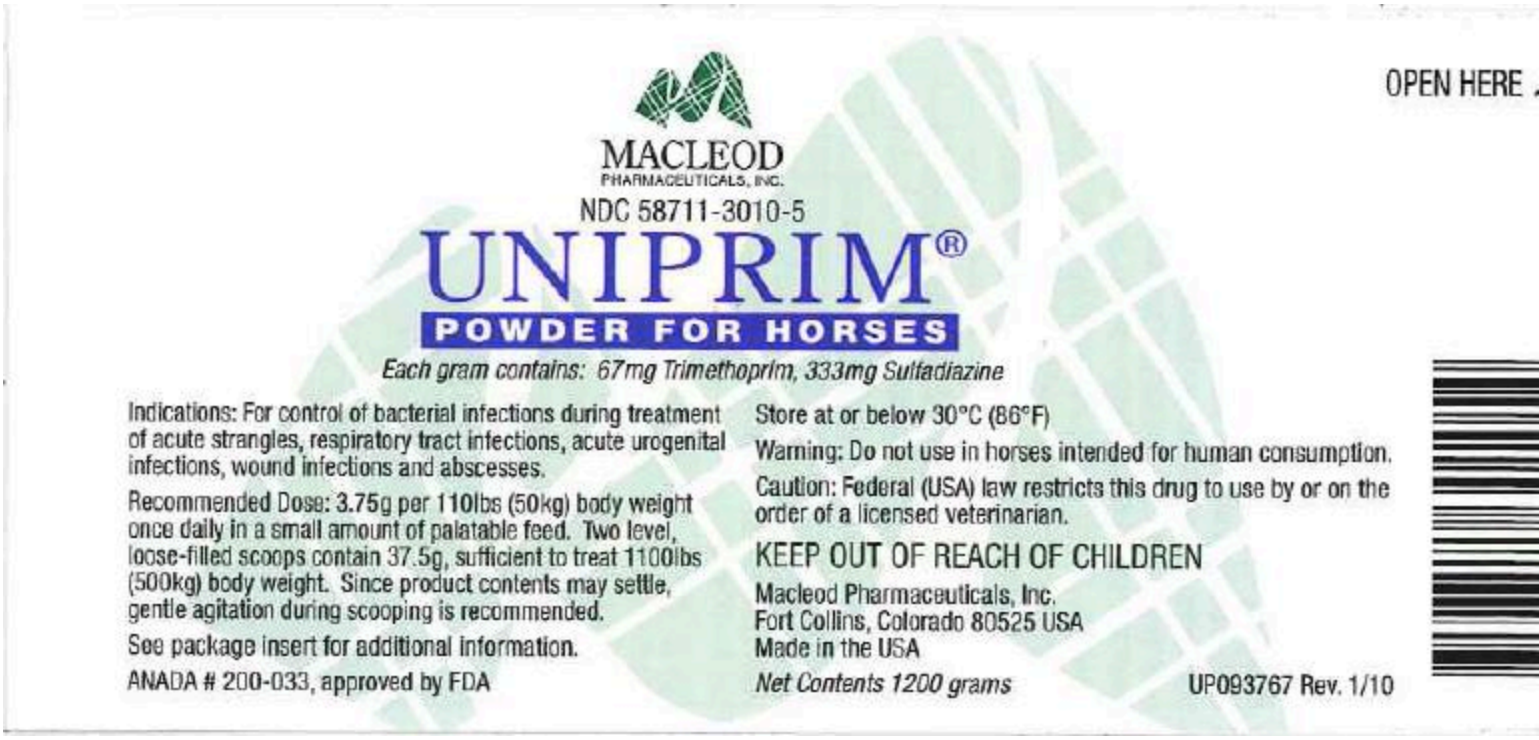
PRINCIPAL DISPLAY PANEL - 1125 G PACKET
MACLEOD PHARMACEUTICALS, INC.

NDC 58711-3010-2
UNIPRIM®
POWDER FOR HORSES
Each g contains: 67mg Trimethoprim, 333mg Sulfadiazine
Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.
Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed. A level scoop contains 37.5g, sufficient to treat 1100lb (500kg) body weight.
Warning: Do not use in horses intended for human consumption.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
KEEP OUT OF REACH OF CHILDREN
Macleod Pharmaceuticals, Inc.
Fort Collins, Colorado 80525 USA
Made in the USA
Net Contents 1125 grams
See package insert for additional information.
Store at or below 30°C (86°F)
ANADA # 200-033, approved by FDA

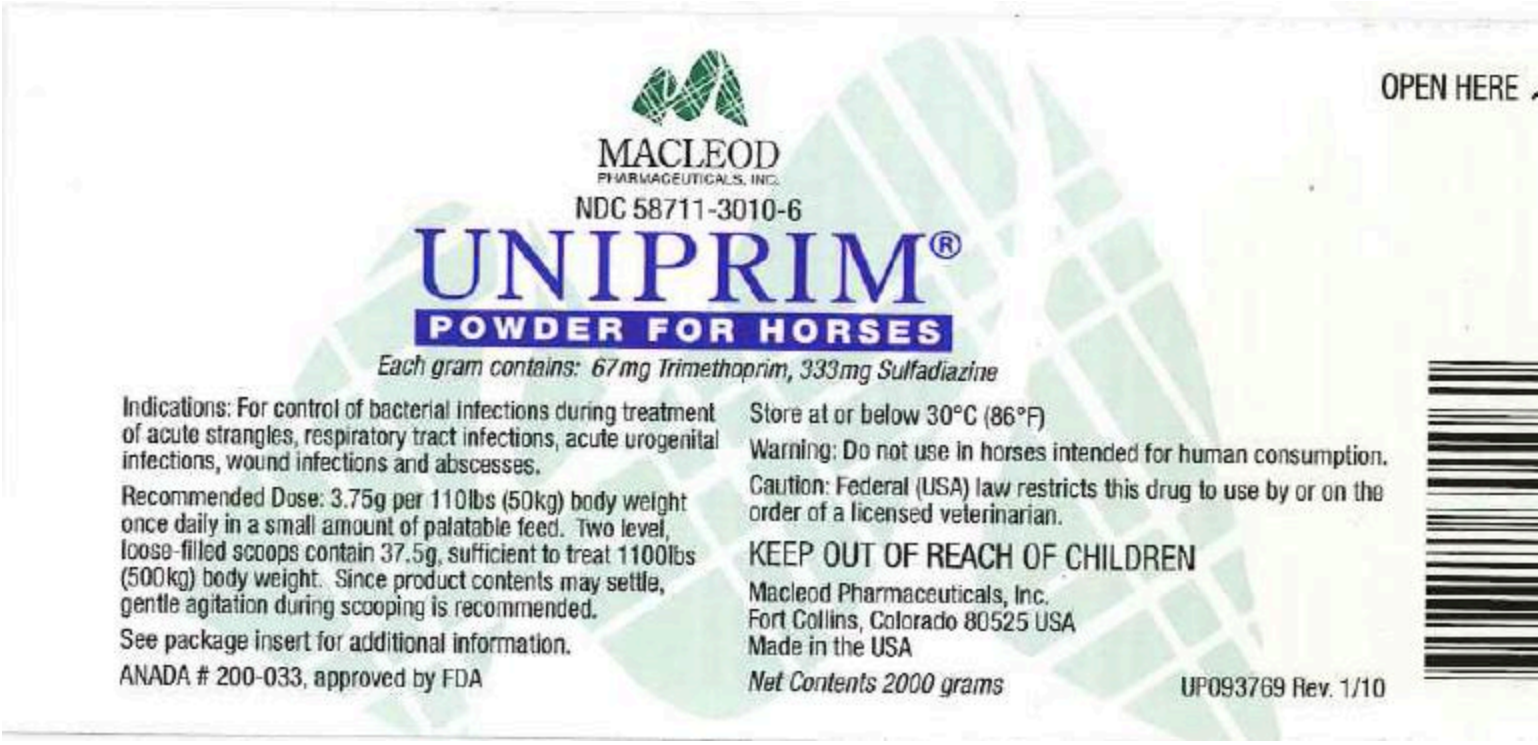
PRINCIPAL DISPLAY PANEL - 37.5 G PACKET
MACLEOD PHARMACEUTICALS, INC.
NDC 58711-3010-1
UNIPRIM™
POWDER FOR HORSES
Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine
Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.
Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed.
Warning: Not for use in horses intended for food.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
KEEP OUT OF REACH OF CHILDREN
Manufactured for
Macleod Pharmaceuticals, Inc.
Fort Collins, CO 80525 USA
Net Contents 37.5 grams
See package insert for additional information.
Store at or below 30°C (86°F)
ANADA # 200-033, approved by FDA

PRINCIPAL DISPLAY PANEL - 1200 G JAR
MACLEOD PHARMACEUTICALS, INC.
NDC 58711-3010-5
UNIPRIM®
POWDER FOR HORSES
Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine
Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.
Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed. Two level, loose-filled scoops contain 37.5g, sufficient to treat 1100lb (500kg) body weight. Since product contents may settle, gentle agitation during scooping is recommended.
Warning: Do not use in horses intended for human consumption.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
KEEP OUT OF REACH OF CHILDREN
Macleod Pharmaceuticals, Inc.
Fort Collins, Colorado 80525 USA
Made in the USA
Net Contents 1200 grams
See package insert for additional information.
Store at or below 30°C (86°F)

ANADA # 200-033, approved by FDA



PRINCIPAL DISPLAY PANEL - 2000 G PAIL
MACLEOD PHARMACEUTICALS, INC.
NDC 58711-3010-6
UNIPRIM®
POWDER FOR HORSES
Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine
Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.
Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed. Two level, loose-filled scoops contain 37.5g, sufficient to treat 1100lb (500kg) body weight. Since product contents may settle, gentle agitation during scooping is recommended.
Warning: Do not use in horses intended for human consumption.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
KEEP OUT OF REACH OF CHILDREN
Macleod Pharmaceuticals, Inc.
Fort Collins, Colorado 80525 USA
Made in the USA
Net Contents 2000 grams
See package insert for additional information.
Store at or below 30°C (86°F)
ANADA # 200-033, approved by FDA



PRINCIPAL DISPLAY PANEL - 200 G JAR
MACLEOD PHARMACEUTICALS, INC.
NDC 58711-3010-4
UNIPRIM®
POWDER FOR HORSES
Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine
Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.
Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed. Two level, loose-filled scoops contain 37.5g, sufficient to treat 1100lb (500kg) body weight. Since product contents may settle, gentle agitation during scooping is recommended.
Warning: Do not use in horses intended for human consumption.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
KEEP OUT OF REACH OF CHILDREN
Macleod Pharmaceuticals, Inc.
Fort Collins, Colorado 80525 USA
Made in the USA
Net Contents 200 grams
See package insert for additional information.
Store at or below 30°C (86°F)
ANADA # 200-033, approved by FDA

PRINCIPAL DISPLAY PANEL - 400 G JAR
MACLEOD PHARMACEUTICALS, INC.
NDC 58711-3010-3
UNIPRIM®
POWDER FOR HORSES
Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine
Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.
Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed. Two level, loose-filled scoops contain 37.5g, sufficient to treat 1100lb (500kg) body weight. Since product contents may settle, gentle agitation during scooping is recommended.
Warning: Do not use in horses intended for human consumption.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
KEEP OUT OF REACH OF CHILDREN
Macleod Pharmaceuticals, Inc.
Fort Collins, Colorado 80525 USA
Made in the USA
Net Contents 400 grams
See package insert for additional information.
Store at or below 30°C (86°F)
ANADA # 200-033, approved by FDA

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MACLEOD
PHARMACEUTICALS, INC.

NDC 58711-3010-3

UNIPRIM®

POWDER FOR HORSES

Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine

Indications: For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections and abscesses.

Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed. Two level, loose-filled scoops contain 37.5g, sufficient to treat 1100lbs (500kg) body weight. Since product contents may settle, gentle agitation during scooping is recommended.

See package insert for additional information.

ANADA # 200-033, approved by FDA

Store at or below 30°C (86°F)

Warning: Do not use in horses intended for human consumption.

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

KEEP OUT OF REACH OF CHILDREN

Macleod Pharmaceuticals, Inc.
Fort Collins, Colorado 80525 USA
Made in the USA

Net Contents 400 grams

UP093765 Rev. 1/10